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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,944	03/22/2001	Keith D. Allen	R-654	8251

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,944	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16 and 22-35* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 11-16 and 22-35 are pending in the application.

Claims 11-16 and 22-25 are withdrawn from consideration as directed to non-elected subject matter.

This Office Action is in response to the Amendment filed on 10/4/02.

The Amendment filed 10/4/02 (Paper No. 13) has been entered. Claims 1-10 and 17-21 have been cancelled. Claims 26-35 have been newly added.

Response to Amendment

The rejection of claims 8 and 17-21 under 35 U.S.C. 112, first paragraph is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-4, 9, 10, 21 under 35 U.S.C. 112, second paragraph is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-10 under 35 U.S.C.102 (b) is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-8 and 10 under 35 U.S.C. 103 (a) is moot in light of Applicants' cancellation of the claims.

The newly added claims 26-35 are rejected under 35 U.S.C. 112, first paragraph as discussed below.

The newly added claims 26 and 27 is rejected under 35 U.S.C. 112, second paragraph as discussed below.

The newly added claims 26-29 and 35 are rejected under 35 U.S.C. 102 (b) as discussed below.

The newly added claims 26-29 and 35 are rejected under 35 U.S.C. 103 (a) as discussed below.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claim Rejections - 35 USC § 112

Claims 25-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous melanocyte stimulating hormone receptor gene knockout mouse that **lacks production of functional melanocyte stimulating hormone receptor protein**, wherein said mouse exhibits hypoactivity, a method of making said mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising melanocyte stimulating hormone receptor knockout construct, introducing said ES cells into blastocyst, and subsequently producing a transgenic knockout mouse, does not reasonably provide enablement for a transgenic mouse comprising any type of disrupted melanocyte stimulating hormone receptor gene, and a method of making said knockout mouse by introducing the knockout construct into any type of cell, or introducing ES cells directly into the pseudopregnant mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is a transgenic mouse comprising a disruption in a melanocyte stimulating hormone receptor gene and exhibiting a phenotype comprising hypoactivity; and a method of making said transgenic mouse. The specification discloses a method for generating said mouse by homologous recombination using a melanocyte stimulating hormone receptor-targeting construct (see page 54-60, examples 1-4). The specification further

discloses that the homozygous knockout mice exhibit the phenotype comprising hypoactivity (see page 59-60, lines 30-36 and line 5-9).

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, col.1 1st paragraph, Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses that a homozygous melanocyte stimulating hormone receptor gene knockout mouse exhibits the phenotype of hypoactivity. The phenotype of a melanocyte stimulating hormone receptor gene knockout mouse is essential for the use of said mouse.

The specification discloses that the word "disruption" comprises altering or replacing a promoter, enhancer, or splice site of a target gene, and can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal product's activity (see page 5, lines 24-27). However, such a broad range of different types of "disruption" would not produce the phenotype as disclosed by the specification, which is disclosed as being dependent upon inactivation of the gene. The specification only discloses a mouse with two alleles of melanocyte stimulating hormone receptor gene disrupted by inserting a selection marker, and said mouse exhibits the phenotype of hypoactivity. Thus, the phenotype of a transgenic mouse comprising a "disruption," as defined by the specification, in a melanocyte stimulating hormone receptor gene is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic knockout mice that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. One skilled in the art

would have to engage in undue experimentation to make and use the invention commensurate in scope with these claims.

The specification teaches a method of making the melanocyte stimulating hormone receptor gene knockout mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising melanocyte stimulating hormone receptor gene knockout construct, introducing said ES cells into blastocyst, introducing the blastocyst into a pseudopregnant mouse, and subsequently generates a transgenic knockout mouse. However, the specification does not support a method of making said mouse by introducing ES cells directly into a pseudopregnant mouse (claim 31). The prior art does not teach such methods either. Therefore, one skilled in the art would have to engage in undue experimentation to make and use the invention commensurate in scope with these claims.

This rejection may be overcome by amending the claims to recite only the transgenic knockout mouse that lacks production of functional melanocyte stimulating hormone receptor protein and exhibits the disclosed phenotype, and provide additional method steps in claim 31.

Claims 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 26 and 27, the term "selectable marker" and "screening marker" render the claims indefinite because it is unclear how a marker protein can be part of a vector construct. It is recommended to use the term "selectable marker gene."

Regarding claim 27, the recitation of "opposite the selectable marker" renders the claims indefinite because it is unclear what the term "opposite" means. In other word, does it mean that the screening marker is in anti-sense orientation of the "selectable marker," at 5' direction or 3' direction of the "selectable marker?" Clarification is needed.

Claim Rejections - 35 USC § 102

Claims 26-29 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Cone et al.(US 6,278,038).

The claims are drawn to a melanocyte stimulating hormone receptor gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a melanocyte stimulating hormone receptor. The recitation of "wherein the target construct when...exhibits hypoactivity" defines the intended use of the knockout construct, which does not carry patentable weight.

Cone et al. disclose the generation of a melanocyte stimulating hormone receptor knockout mouse by homologous recombination using a targeting construct (see col. 22-30, example 4 and 5) and subsequent analysis of phenotype of said mouse. Cone et al. also disclose that immortalized cell line can be derived from tissues and organs of said knockout mouse. Therefore, Cone et al. disclose the instant claimed inventions.

Applicants argue that Cone et al. do not anticipate the claims because Cone et al. do not disclose a melanocyte stimulating hormone receptor knockout mice with a hypoactive phenotype. However, the present claims are drawn to a melanocyte stimulating hormone receptor gene-targeting construct and a method of making said construct. The claims are further

drawn to a cell comprising a disruption in a melanocyte stimulating hormone receptor. The recitation of "wherein the target construct when...exhibits hypoactivity" defines the intended use of the knockout construct, which does not carry patentable weight. Therefore, the Cone reference anticipate claims 26-29 and 35.

Claim Rejections - 35 USC § 103

Claims 26-29 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Mountjoy et al. (1992, Science vol. 257, 1248-1251) and Adachi et al (1999, J. Immunology, vol.163: 3363-3368).

The claims are drawn to a melanocyte stimulating hormone receptor gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a melanocyte stimulating hormone receptor. The recitation of "wherein the target construct when...exhibits hypoactivity" defines the intended use of the knockout construct, which does not carry patentable weight.

Mansour et al. teach a strategy for targeted disruption of the hprt and proto-oncogene int-2 in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from hprt and int-2 respectively, and a neo selection marker in between the two sequences (see page 350, figure

3). However, Mansour et al. do not teach how to make a melanocyte stimulating hormone receptor gene target construct and knockout mouse.

Mountjoy et al. teach the cloning of mouse melanocyte stimulating hormone receptor gene. They provide the cloned coding sequence for melanocyte stimulating hormone receptor gene (see page 1249, figure 2 legend, accession number X65633-5).

Adachi et al. teach that melanocyte stimulating hormone receptor is expressed on a stimulated mast cell line and melanocyte stimulating hormone alpha inhibits histamine release form mast cells (see page 3367, col. 1, lines 4-16). Adachi et al. also teach that melanocyte stimulating hormone alpha may be involved in stimulating cell proliferation in the presence of IL-3 (see page 3367, 2nd col. Lines 7-11). Adachi et al. further teach that melanocyte stimulating hormone alpha affects cytokine production in inflammatory tissue (3367, 2nd col., 2nd paragraph).

It would have been obvious to one in the ordinary art to make a melanocyte stimulating hormone receptor gene knockout construct in order to make a melanocyte stimulating hormone receptor gene knockout mouse. The ordinary artisan would have been motivated to knockout the function of melanocyte stimulating hormone receptor gene in a mouse to study the role melanocyte stimulating hormone alpha plays in cell proliferation and tissue inflammatory response (See Adachi, 3367, 2nd col., 2nd paragraph). The ordinary artisan would have had reasonable expectation of success because of the teachings of Mansour et al., who teach a general method of generating gene targeting construct for targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Mountjoy et al., who teach the coding sequence of the mouse melanocyte stimulating hormone receptor gene, and Adachi et al., who teach the importance of this gene in regulating cell proliferation and cytokine

production in inflammatory response. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argues that non of the references above teach a method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Although non of the three reference individually teach a method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene, the combined teaching suggest to make such a mouse to study the function of this gene. The Adachi reference has given the motivation to study this gene, the Mansour and Mountjoy references have provided reasonable expectation of success to make said knockout mice. Therefore, the invention would have been obvious to one of ordinary skill of art at the time the invention was made.

Conclusion

Claims 26-35 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
November 18, 2002

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER